Noise in genetic and neural networks

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Both neural and genetic networks are significantly noisy, and stochastic effects in both cases ultimately arise from molecular events. Nevertheless, a gulf exists between the two fields, with researchers in one often being unaware of similar work in the other. In this Special Issue, we focus on bridging this gap and present a collection of papers from both fields together. For each field, the networks studied range from just a single gene or neuron to endogenous networks. In this introductory article, we describe the sources of noise in both genetic and neural systems. We discuss the modeling techniques in each area and point out similarities. We hope that, by reading both sets of papers, ideas developed in one field will give insight to scientists from the other and that a common language and methodology will develop. © *2006 American Institute of Physics*.
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I. INTRODUCTION

Biological systems are successful despite existing in a stochastic environment. Experimentalists and modelers, however, are just beginning to unravel the intricate interplay of noise with determinism in these systems. They are guided by an increasing number of theoretical, computational, and experimental tools. Each strand of biology has been successful with a subset of these techniques, but the areas of neural and genetic networks are of particular note. Nevertheless, for whoever reads the neural or genetic literature, it is clear that there exists an intellectual divide: with few exceptions, they do not cite each other.

This issue aims to help bridge this gap. We hope that bringing together representative research from each area will allow an idea born in one field to bring new insight to the other. At the same time, we wish to encourage the development of a common language, especially as the two areas are not isolated *in vivo*: neural activity often influences cell signaling and so gene expression, and vice versa.

Noise has multiple sources.[1] In any experimental or modeling effort, a challenge is to unambiguously identify these sources. Indeed, noise in one system may be considered as dynamics in another. For example, determining how ion channels affect the firing patterns of a neuron is a complex area of research. Yet, for the study of neural networks, only the coarse features of these stochastic patterns may be necessary to explain network oscillations. The challenge of appropriately bridging spatiotemporal scales is a central theme of the issue.

Out of the numerous deserving contributors, we have chosen studies where there is a direct link to real data. In fact, it is often when confronted with real data, and the variability of biological responses that one feels compelled to use a stochastic approach. New experimental techniques are driving understanding, and models can now be directly compared with experiment. Molecular biology has been revolutionized by the development of noninvasive, fluorescent reporters and, indeed, they have allowed stochastic gene expression to be quantified *in vivo*.[2–5] Today's challenge is to understand the consequences of such stochasticity for cellular "design": is noise a hindrance, potentially degrading the function of biochemical networks, or is it a source of variability that cells exploit?

Neuroscience has also benefited from experimental developments. One can now visualize synaptic events in neuron dendrites as well as waves of calcium activity permeating a neural network. Neuroscientists have access to relatively long and clean time series of neural activity, even though it is still difficult to simultaneously monitor many neurons. Such data are beginning to appear for genetic systems,[6] but the time intervals between measurements are much longer, limiting the types of analysis. In both areas, the traditional approach has been to scrutinize the mean response, but there is a subculture of scientists dedicated to finding significance in the variance itself.

In this paper, we describe the sources of noise in both neural and genetic networks, the modeling methods used, and discuss parallels and similar problems. Finally, we present the articles of the issue. We hope that by reading both sets of papers, researchers in each field will see both new synergies and new challenges.

II. SOURCES OF NOISE

A. Noise in genetic networks

The potential importance of noise in molecular biology has long been recognized,[7] but it is only within the last decade that stochastic effects have been unambiguously measured during gene expression in both bacteria[2,3] and

eukaryotes.[4,5] At the same time, the rediscovery of the Gillespie algorithm[8] and the availability of large amounts of *in vivo* data, has led to a new recognition of the importance of modeling and quantitative data analysis in both the experimental and theoretical communities, spawning the new field of "systems biology." The seminal modeling papers demonstrating that stochastic effects could alter cellular phenotypes were those of Arkin, McAdams, and co-workers.[9,10] Since then, synthetic biology has allowed theoretical conjectures to be tested in living cells,[11,12] and there has been an explosion in both modeling and experimental work. See Refs. 13–15 for reviews.

Gene expression is a complex, two stage process. First, the DNA of the gene is transcribed into messenger RNA (mRNA) by the enzyme RNA polymerase: the information stored in the nucleotide order on the DNA is copied into information stored by the nucleotide order on the mRNA. An expressed gene can give rise to several mRNA transcripts. Second, the mRNA is translated into protein by enzymes called ribosomes: the information stored in nucleotides on the mRNA is translated into the amino acids of the protein. Several ribosomes can bind to and translate a single mRNA simultaneously. In our own cells, an entire mRNA is transcribed, processed in the nucleus, and then exported to the cytosol for translation. In bacteria, which have no nucleus, translation occurs as soon as part of the mRNA is transcribed.

A region of DNA called the promoter controls transcription, and so gene expression. An unregulated gene, said to be constitutively expressed, is shown in Fig. 1(A) for a bacterium. The promoter contains only a binding site for RNA polymerase. Nearly all genes *in vivo*, however, are regulated. Proteins, called transcription factors, are able to bind to operator sites in the DNA of the promoter region. Once bound, they either hinder the binding of RNA polymerase to the promoter [Fig. 1(B)] and so repress gene expression—the transcription factors are then called repressors—or they encourage the binding of RNA polymerase to the promoter [Fig. 1(C)] and activate gene expression—the transcription factors are then called activators. Any particular promoter can often be bound by both activators and repressors, leading to gene expression that can be a highly nonlinear function of the transcription factor concentration.

A further level of control is that the transcription factor's ability to bind DNA can be a nonlinear function of the concentration of another molecule, called an inducer. For example, the *lac* operon in *Escherichia coli* encodes enzymes to import and digest the sugar lactose (an operon is a collection of genes that are encoded end to end on the DNA and consequently are all transcribed into a single mRNA). The operon is repressed by a transcription factor called the *lac* repressor in the absence of intracellular lactose. Sensibly, there is very little expression if no lactose is present. If some lactose does enter the cell, it binds the *lac* repressor and by doing so reduces the ability of the *lac* repressor to bind DNA. For high amounts of intracellular lactose, all the *lac* repressors are bound by lactose and none bind DNA. The *lac* operon is then expressed, and the cell synthesizes enzymes able to digest the lactose present. The levels of lactose ultimately control expression, with high levels of the inducer lactose inducing expression.

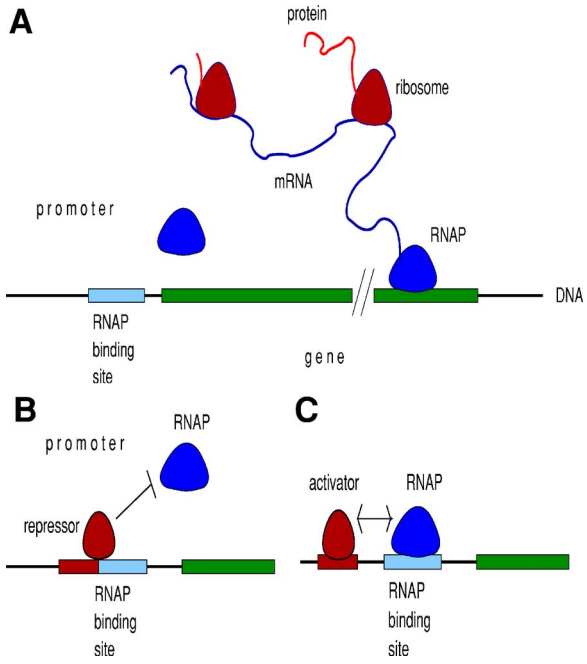

FIG. 1. Gene expression in bacteria. (A) Constitutive (unregulated) expression. RNA polymerase (RNAP) binds to the promoter at a free RNAP binding site. It initiates transcription and moves down the DNA of the gene. Ribosomes bind to and start translating the mRNA into protein as soon as part of the mRNA is transcribed. Once it reaches the end of the gene, RNAP dissociates from the DNA, but another RNAP may have already initiated an additional round of transcription. Similarly, many ribosomes often translate the same mRNA. (B) Negative regulation. A repressor transcription factor has a binding site in the promoter region. This site overlaps the RNAP binding site and so if a repressor is bound, its presence physically prevents RNAP from binding to the promoter: there is no gene expression. (C) Positive regulation. For a gene with a weak RNAP binding site, very little transcription occurs. When an activator transcription factor is also able to bind to the promoter, its presence can increase the free energy of RNAP binding and so it can enable high rates of transcription.

Most transcription factors in bacteria consist of two identical proteins bound together—they are then called dimers—or sometimes of four identical proteins bound together—they are then called tetramers. Such multimers aid the recognition of DNA binding sites and contribute to the nonlinearity in expression of a gene as the inducer changes. Each protein in the multimer can potentially bind to the inducer and, through what is known as an allosteric interaction, the binding of an inducer to one protein in the multimer increases the probability that an inducer will bind to another protein in the multimer. Thus the transition of a transcription factor from being able to bind DNA to being unable to bind DNA can be a very steep sigmoidal function of the inducer concentration. Such non-linearities are often referred to as cooperativities, because one protein "cooperates" with the other to help it bind to the inducer.

All these processes are chemical reactions and so are potentially significantly stochastic. Reacting molecules come together by diffusion, their motion driven by random collisions with other molecules. Once together, such collisions randomly alter the internal energies of the reactants and so their propensity to react. Such stochastic effects, however,

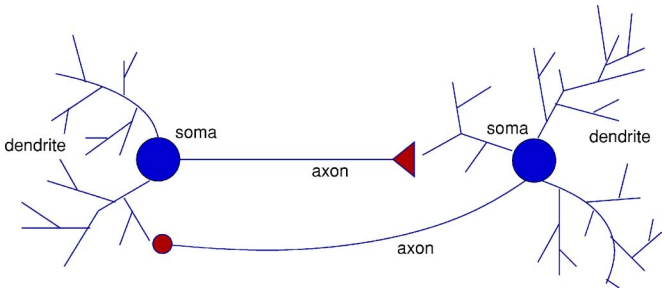

FIG. 2. Two neurons connected to one another via feedback. A neuron receives input in the form of current through its synapses. Dependent on the ion channels involved, these currents propagate in a linear or nonlinear fashion to the soma. When the voltage at the soma of the left neuron exceeds a threshold, the soma fires an action potential that is transmitted both down the axon to the neuron on the right and to its own dendrites. The triangle represents an excitatory connection from the left to the right neuron. The right neuron is connected to the one on the left via an inhibitory synapse. Noise from dendritic input from other neurons or from conductance fluctuations of ion channels is present in all parts of this diagram, although much less in the axon.

are only important when mean numbers of molecules are low. Then, individual reactions, which at most change the numbers of molecules by one or two, matter. This stochasticity is referred to as intrinsic noise as it is inherent in the dynamics of any biochemical system.

It is not just the stochasticity intrinsic to a cellular process that generates variation; other cellular processes are also fluctuating and interact with the process of interest. The variation generated in this way is termed extrinsic noise.[3,16] There are numerous extrinsic variables. For example, as a cell grows, the number of ribosomes and the variance in the number of ribosomes can change altering the noise in gene expression. Similarly, fluctuations in the numbers of nutrients in the extracellular environment, in the temperature, in the number of amino acids available intracellularly, etc., could all influence gene expression. Experimentally, in fact, it is the extrinsic noise that dominates intrinsic noise and sets cell-to-cell variation.[3,5]

B. Noise in neural networks

Noise entered theoretical neuroscience many decades ago. The first Boolean model of McCullough and Pitts for logical computing in neural networks was quickly enlarged to include stochastic effects. Early works on this model and others are in the collected papers in Refs. 17 and 18. An excellent overview of the first literature on stochastic neural modeling can be found in Refs. 19 and 20. A more recent review is Ref. 21.

Figure 2 illustrates the main components of a neuron. Noise occurs in each part. A neuron has a transmembrane potential of approximately −70 mV, with the inside being more negative than the outside. This polarization is maintained via ion pumps driven by metabolic energy. A typical neuron integrates current from incoming sources, approximately like an RC circuit. Via axons that end in chemical synapses, it connects to other, "postsynaptic," neurons. The "presynaptic neuron" only affects postsynaptic neurons if its voltage "depolarizes" sufficiently (becomes more positive) to open fast ion channels. The opening of these channels is a regenerative or positive feedback process: channel openings cause further depolarization that opens more channels. The result is an explosive depolarization that activates other kinds of channels that repolarize the membrane within a few milliseconds. Known as the action potential, the resulting sharp spike in voltage propagates along an axon that branches and often ends in hundreds of synapses onto other neurons. The arrival of the spike triggers a release of a chemical ″neurotransmitter″ that opens ion channels in the postsynaptic neurons. Neural networks thus combine elements of analog and digital communication.

Chemical synapses are not deterministic switches that convert incoming spikes into the release of fixed packets of neurotransmitter. Instead, they are characterized by a probability of transmitter release and often release a transmitter at some low rate, even without any incoming spikes. The probability of release depends on the history of firing of both the pre- and the postsynaptic neuron: once a neuron fires, it affects every location in the neuron, including receptors at its incoming synapses. Information flow is thus not unidirectional across synapses. Many neurons are also electrically coupled via protein structures called gap junctions that allow the exchange of ions between different cells.

For a single neuron, the time evolution of the membrane potential is governed by equations of the so-called Hodgkin-Huxley (HH) formalism (see Ref. 22 for an introduction). This deterministic, nonlinear system of equations describes the "known" mean activation and inactivation behavior of various ion channels in response to voltage, ions, and some other chemicals. The qualifier "known" is important: often only partial knowledge of the ion channels is available, involving painstaking, intracellular measurements with microelectrodes. In many cases, we have only extracellular recordings of cells, and must surmise their workings from the times at which they fire in response to stimuli and from the effects of various drugs on these responses. Nevertheless, the HH formalism often predicts neural response to deterministic inputs, such as injected current, or to intrinsic noise sources, such as conductance fluctuations, and to extrinsic noise sources, such as a synapse. The HH equations are complex, usually four or more coupled highly nonlinear ordinary differential equations, and their behavior in the presence of noise as well as for some deterministic cases is not well understood. The deterministic behavior is often best characterized in *in vitro* "slice" preparations, which are devoid of much of the synaptic noise from other neurons.

The genetic noise described previously is a source of variability within the neuron, but its effect on neuron firing has barely been explored. Rather, researchers have focused on noise sources that act on faster time scales: in ion channels and pumps, which control ion flow across the plasma membrane;[23] at synapses, which mediate connections between neurons; in whole neurons, via the summed currents flowing through ion channels; in neural networks, where the noise is related to the activity of all neurons impinging on a given neuron; and in brain rhythms, generated by millions of neurons interacting across large spatial scales. The dominant source is usually synaptic noise, i.e., noise coming from the

activity of other neurons. Synaptic strengths also fluctuate because of the different availabilities of neurotransmitter and of components of various biochemical signaling pathways. Noise on longer time scales arises from the long-term modulation of neural activity by "neuromodulators" such as serotonin. A recent review of neuronal noise, particularly for sensorimotor control, can be found in Ref. 24.

III. A COMMON METHODOLOGY

Although there are many concepts common to both areas, they often go under different names. Interactions between genes or neurons, including self-interactions, have two polarities: positive and negative. One neuron can excite another, enhancing its probability to fire; one gene may cause activation of another, increasing its probability to express (strictly, the protein product of one gene activates the transcription of another gene). Alternatively, one neuron can inhibit another neuron, and one gene can cause the repression of another gene. The conductance of an ion channel can be modulated by voltage or agonist molecules; similarly, the DNA binding properties of a transcription factor can be modulated by the binding of an inducer.

In both areas, positive feedback is often associated with bi- or multistability, and negative feedback with homeostasis and oscillation. Both systems operate with delays: in neuroscience, delays come from the finite speed of propagation down axons, or to integration of currents in synapses or circuits that are not being modeled explicitly; in bacteria, it typically takes 3 min to synthesize a protein once RNA polymerase initiates transcription. Noise in both areas is ultimately generated by molecular events, and the coefficient of variation, the ratio of standard deviation to the mean of a distribution, is a common measure of variability. They also share the language of dynamical systems to characterize different behaviors, including the concept of "bursting," where proteins are translated and action potentials fired in bursts, and the language of engineering to characterize network design and function, such as groups of neurons or motifs of genes that act as switches, amplifiers, oscillators, etc.

IV. HIERARCHY OF MATHEMATICAL MODELS

In both genetic and neural networks, similar mathematical models are used. If the noise is intrinsic, a master equation governing the time evolution of the probability of the states of the system is adopted. If the noise is extrinsic, acting on the system of interest, noise terms are added to the deterministic equations.

A. Genetic networks

For any system of biochemical reactions, the ultimate level of description is the chemical master equation. This equation describes how the probability changes with time for any state of the system, where each state is defined by the number of molecules present of each chemical species. The master equation contains the deterministic, differential equation approximation that is often used to describe system dynamics: the mean of each chemical species obeys these deterministic equations as the numbers of molecules of all species increase. The master equation itself is analytically solvable only for systems with first-order reactions. Nevertheless, several approximations exist, all of which exploit the tendency of fluctuations to decrease as the numbers of molecules increase. The most systematic (and complex) is the linear noise approach of van Kampen.[25] If the concentration of each chemical species is fixed, then changing the system size (system volume), Ω, alters the number of molecules of every chemical species. The linear noise approximation is based on a systematic expansion of the master equation in Ω^{-1}. It leads to Fokker Planck-like equations that accurately describe small fluctuations around the stable attractor of the system. For systems that just tend to steady state, a Langevin approach is also often used.[26,27] Here white noise terms are added to the deterministic equations, with their magnitude being determined by the steady-state chemical reactions. At steady state, the Langevin and linear noise approaches are equivalent. Unfortunately, all these methods usually become intractable once the number of chemical species in the system reaches more than three (one then needs analytical inversions of 4×4 matrices or a calculation of their eigenvalues). Rather than numerically solving the master equation, the Gillespie algorithm,[8] a Monte Carlo method, is often used to simulate one sample time course from the master equation. By doing many simulations and averaging, the mean and variance for each chemical species can be calculated as a function of time.

B. Neural networks

At the smallest length scale, noise is set by ions moving through ion channels as voltage gradients, chemical gradients, or channel configurations change. Often the channels have a number of structural configurations, each with its own conductance, and a master equation can be used to calculate the mean rates of transition between states. These rates are usually estimated directly from data. Channel conductance can then be incorporated into a kinetic description for the membrane voltage, often following the deterministic HH formalism. By using the state-transition diagrams of ion channels to model fluctuations in channel conductance, Langevin-type HH equations, i.e., HH equations that properly account for channel noise, can also be derived. The analytical determination of the properties of the membrane fluctuations and of the firing rate of such complex models is currently beyond reach. One thus resorts to numerics, or theory on simplified models such as the integrate-and-fire model, a first-order ordinary differential equation—it is linear, except for the reset of the potential whenever it hits a fixed threshold.

The study of membrane voltage fluctuations has in fact received considerable attention in the context of simplified HH models (see Ref. 20 and references therein). When the dominant source of noise is assumed to be synaptic input, the noise from incoming spikes is often approximated by Gaussian white noise—the so-called "diffusion approximation." The membrane voltage then evolves as an Ornstein-Uhlenbeck process, with the added twist, however, of an absorbing boundary at the threshold voltage. A particularly difficult challenge in this area is to identify the stochastic differential description that also properly accounts for the

discrete nature and statistics of these incoming spikes (shot noise) at synapses onto a neuron. The articles of Dorval *et al.*, Richardson and Gerstner, and Shuai and Jung herein discuss the complexity of these issues. The firing properties of more realistic versions of these models, such as ones that include the smooth synaptic response to a spike (see, e.g., Ref. 28), or that better represent the bifurcation from quiescence to periodic firing as a saddle-node bifurcation (the so-called quadratic integrate-and-fire model; see, e.g., Ref. 29), are keeping a number of theorists busy.

It is also expected that many of the effects observed in nonlinear stochastic systems will be seen in neural (and genetic) systems, and that similar theoretical approaches will be applicable—see, e.g., Ref. 30, which includes specific examples on neural and genetic noise. In fact, there is significant interest in noise in excitable systems,[31] where the interactions of noise with nonlinearities leads to novel and even paradoxical behaviors. For example, noise can propagate signals in excitable media,[32] improve memory (see the paper of Senn and Fusi in this issue), and increase signal-to-noise ratios via stochastic resonance.[33,34] Research into the synchronization properties of neurons, given their noisy dynamics, has further benefited from recent advances in stochastic synchronization theory.[35]

A number of formalisms have emerged in recent years to characterize the firing activity in populations of stochastic neurons, and to efficiently compute these properties in network simulations (see, e.g., Refs. 36–40). The analyses use a range of techniques from mean field theory and linear response theory, often incorporating the mean firing rate of a single neuron obtained via first-passage time calculations (i.e., Fokker-Planck-type analyses). Some also include the fact that the variance of the noise in a network of spiking neurons is a function of the mean firing rate, with the consequence that the noise intensity becomes a dynamical quantity when the mean is time dependent, as occurs e.g., during network oscillations.

These formalisms also propose a variety of ways to deal with time delays. A major difficulty arises in fact when describing non-Markovian effects such as delays or memory in nonlinear systems, for which theory is only emerging. In a noiseless world, delays lead to either nonlinear delay-differential or to integrodifferential equations, depending on their range of values. Delays are often used to simplify the description of the spatial propagation of a signal. For example, by using a delay one can avoid the partial differential equations describing propagation of spikes along an axon.

Chaos is predicted in certain kinds of neural networks,[41] and so is another potential source of stochastic-like effects. There have also been recent studies of how noise propagates in feedforward networks,[42,43] a novel area of investigation in genetic networks as well.[44] Finally, a more benign yet still important form of noise arises from inhomogeneities of parameters in a network, such as synaptic connection strengths. These inhomogeneities, also present in the parameters of genetic networks, can have important consequences for network synchrony.

V. THIS ISSUE

The contributions in this issue reflect the perhaps more established role that noise has in neuroscience. In genetic networks, the initial focus has been understanding noise in simple systems of one or a few genes. Here, this approach is taken by Cox *et al.*, who consider a single autoregulatory gene, and Tsimring *et al.*, who discuss ways to analyze intrinsic and extrinsic noise in simple gene networks.

For neural systems, noise ultimately originates from ion channels and synapses: Shuai and Jung look at fluctuations in clusters of ion channels; Dorval *et al.* model how synaptic inputs determine the variability and reproducibility of neural firing; and Richardson and Gerstner study the differences between the effects of shot noise synaptic input and its Gaussian white noise limit on membrane potential fluctuations.

Synthetic biology allows three or four gene networks to be constructed *in vivo*. Such networks are ideal for understanding and exploring the cell, particularly where dynamical behavior designed into the network does not occur *in vivo* or occurs substantially modified. Scott *et al.* analyze the oscillatory behavior of two synthetic oscillators and Hooshangi and Weiss study how noise propagates through genes arranged in a cascade.

A similar level of complexity on the neural side is explored by Miller and Wang, who study the stability of long term memory despite noise affecting the molecular components of synapses and the firing patterns of short term memory.

Understanding noise in endogenous genetic networks is only beginning, and Gonze and Goldbeter present an analysis of networks that generate circadian rhythms. In neural networks, the properties of large networks have been much more explored: Neiman *et al.* consider methods to determine the directionality of coupling between two biological oscillators; Senn and Fusi discuss how the incorporation of noise that mimics the probability of neurotransmitter release at synapses leads to enhanced memory storage and retrieval in neural nets; and Chen *et al.* discuss an analysis of the large scale responses of neural networks.

Together the contributions highlight the challenges of working at the interfaces of physics and biology. Unlike physics, theory in biology is in its infancy and is still proving its worth to a science dominated by experiment. Models will have little impact unless closely tied to experimental data. Yet the sheer complexity of biology, whether in genetic or neural networks, necessitates computational approaches. It is only a computer model that can store and integrate all the data now available about particular systems; it is only with simulation that the counterintuitive behaviors of these systems can be understood; and it is only with theory that biological principles will be discovered—principles essential to going beyond the complexity and see how evolution has designed these systems. We hope that this issue will provide synergy between studies of genetic and neural networks, and help pave the way toward both design principles and quantitative, predictive models.

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